ACC.11
60th Annual Scientific Session & Expo

E2045
JACC April 5, 2011
Volume 57, Issue 14

YOUNG INVESTIGATORS AWARDS

MICRORNA-MEDIATED REGULATION OF SMAD1 IN THE VASCULAR ENDOTHELIUM PROMOTES CELL GROWTH ARREST

ACC Special Session
Ernest N. Morial Convention Center, Room 215
Sunday, April 03, 2011, 8:15 a.m.-8:30 a.m.

Session Title: Young Investigators Award Competition: ACCF/Herman K. Gold Young Investigator's Award in Molecular and Cellular Cardiology
Abstract Category: Molecular and Cellular Cardiology
Presentation Number: 0406-06

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Background: Neoangiogenesis is critical for tissue repair in response to injury such as myocardial infarction (MI). The function of microRNAs in vascular endothelial cell (EC) growth and angiogenesis remains poorly understood.

Methods and **Results:** We undertook a microarray profiling approach to assess global patterns of microRNA expression in human umbilical vein endothelial cells (HUVECs) and identified miR-26a as being one of the most differentially regulated under pro-angiogenic conditions. The pro-angiogenic stimuli TNF-α or BMP2 reduced miR-26a expression, whereas TGF-β, which induces growth arrest, increased miR-26a expression. Using bioinformatics approaches, we identified potential miR-26a target genes including Smad1, a critical upstream modulator of Id1. Id1 is known to inhibit the cell cycle inhibitors p21WAF/CIP or p27 in ECs. Our studies demonstrate that miR-26a inhibits Smad1 expression by binding to its 3'-UTR, an effect that decreased Id1 and increased p21WAF/CIP and p27 in HUVECs. Functionally, overexpression of miR-26a markedly induced cell cycle arrest, inhibited migration, reduced the release of the pro-angiogenic factors VEGF or TSP1, and impaired network tube formation in matrigel, whereas blockade of miR-26a had the opposite effects. Using matrigel plug assays in vivo, overexpression of miR-26a potently reduced angiogenesis, whereas inhibition of miR-26a enhanced angiogenesis. In a mouse model of MI, systemic intravenous administration of LNA-antagomiR-26a, which specifically inhibited miR-26a in vivo, resulted in increased blood vessel formation compared to mice that received scrambled control antagomiR injections. Importantly, mice that received the LNA-antagomiR-26a had significantly reduced infarct size compared to mice that received control antagomiRs. Finally, both mice with MI and patients with acute coronary syndromes had increased circulating levels of miR-26a versus sham or healthy controls, respectively.

Conclusions: These findings suggest that targeting miR-26a may provide a novel therapeutic target to promote angiogenesis in physiological or pathological disease states such as MI.